advance the prosecution, claim 11 has been canceled without prejudice. Therefore, withdrawal of this rejection is respectfully requested.

**II. Rejection of Claims Under 35 U.S.C. 102(e)**

Claims 1 and 9 have been rejected under 35 U.S.C. 102(e) as being anticipated by Impraim et al. (US Patent 6,228,578). The Examiner suggests that this reference teaches a method for detecting an oligonucleotide in a body fluid by contacting the fluid with a probe complementary to the oligonucleotide wherein the probe comprises a detectable marker and a binding moiety, placing the fluid in contact with a solid support to which the binding partner is attached, contacting the fluid with a single strand specific nuclease to degrade non-hybridized oligonucleotides and detecting a label associated with the marker. Applicants respectfully traverse this rejection.

At the outset, claim 1, and by dependency claims 2-10, are amended to recite that the method of the present invention consists of these steps.

Impraim et al. (US Patent 6,228,578) describes a non-radioactive hybridization assay and kit for detection of genetic defects, microbial infections or viral infections. In their

method, several specific steps are specified. These include first hydrolyzing the RNA in the sample and denaturing the target DNA that is to be detected, next hybridizing the target DNA sequence to a complementary RNA probe to form a double-stranded DNA/RNA hybrid, next capturing the hybrid onto a solid phase where an anti-hybrid antibody has been immobilized, then eliminating non-hybridized probe by digestion with RNase, and finally detecting the bound hybrid. Therefore, this method specifically teaches a nick and denaturing step and a detection step using a conjugate of a monoclonal antibody that are not the invention as now claimed. MPEP 2131 states that in order to anticipate a claim the reference must teach each and every limitation of the claim. Accordingly, Impraim fails to the teach the method of the present invention which does not include a nick and denature step. Withdrawal of this rejection is therefore respectfully requested.

**III. Rejection of Claims Under 35 U.S.C. 103(a)**

Claims 3, 8 and 11 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Temsamani et al. (1993) in view of Impraim et al. (US Patent 6,228,578). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill in the art to modify the method of Temsamani et al. with the method of

Impraim et al. to teach detection of oligonucleotides by forming hybrids, contacting with a solid support, using a nuclease to degrade non-hybridized probes and then detecting the bound hybrid. Applicants respectfully traverse this rejection.

The claims as amended recite that the method involves a probe that is both a detection probe and a binding moiety and that both single-stranded and double-stranded oligonucleotide moieties are bound to the solid support, with only double-stranded moieties being detected after treatment of the solid support with a single-strand specific nuclease. Support for these amendments is found throughout the specification as filed but in particular at Figure 1 and at page 4, lines 31-35.

Temsamani et al. (1993) disclose a method for quantitation and detection of phosphorothioate modified oligonucleotides. The first step in this method, is explicitly stated in the abstract and shown in Figure 3 as being immobilization of the oligonucleotide to a solid support, in this case a nylon membrane, before the oligonucleotide is contacted with any type of binding probe. Therefore, the oligonucleotide, unmodified, is attached. In the present method, the claims recite and the specification teaches that the binding moiety of the probe, not the oligonucleotide itself, is what binds directly to the solid support. Further,

Temsamani et al. fails to teach, the use of a nuclease of any type to degrade non-hybridized probes. Therefore, this reference does not teach the instant claims which recite contact of a solid support only after hybridization of the oligonucleotide as well as use of a single-strand specific nuclease to degrade non-hybridized probe.

Impraim et al., as discussed *supra*, teaches a method for detection of nucleic acid segments from DNA of organisms such as bacteria and viruses and detection of genetic defects, microbial infections or viral infections by detecting such pieces of DNA (see abstract of Impraim et al. and *Background of the Invention* section). Therefore, Impraim et al. is non-analogous art in accordance with MPEP 2141.01(a). One of skill would not look at such art for guidance in developing a method to detect oligonucleotides in body fluids. Further, Impraim et al. does not specify binding of both double-stranded and single-stranded oligonucleotide moieties to a solid support and does not teach or suggest combining into a probe both the use as a detection device and a binding moiety. In the case of Impraim, it is specified that binding moieties are monoclonal antibodies specific to the DNA:RNA hybrid and detection is due to use of a chemiluminescent substrate for alkaline phosphatase. Nowhere does Impraim et al. teach or

suggest use of a probe that has both binding and detection properties without further steps being added to the method. Nor would one of skill seek to add such steps given the different uses of these methods.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended. Further, one of the references relied upon to establish a *prima facie* case is from non-analogous art. Therefore, there would no motivation for one of skill to modify the method of Temsamani et al. as suggested. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 2 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Temsamani et al. and in view of Impraim et al., and further in view of Serres et al. The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to

combine the oligonucleotide detection method of Temsamani et al., as modified by Impraim, with the method of Serres et al. for detecting oligonucleotides in plasma. Applicants respectfully traverse this rejection.

As discussed *supra*, the primary reference of Temsamani et al. (1993), when combined with the reference of Impraim et al., fails to teach the claimed invention. Therefore, adding Serres et al., which teach detection of oligonucleotides in plasma by another, very different method cannot render the instant invention obvious. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended and withdrawal of this rejection is respectfully requested.

Claims 4-5 and 11 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Impraim et al., in view of Lind et al. (1998). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill to combine the oligonucleotide method of Impraim et al. with the Lind et al. method for modification of oligonucleotides with at least one sugar moiety at the 2' position. Applicants again respectfully traverse this rejection.

As discussed *supra* in Section II, the primary reference of Impraim et al. fails to teach the limitations of the claimed

invention. Therefore, the combination of a secondary reference (Lind et al.) which teaches only methods for modifying oligonucleotides does not render the instant invention obvious. Withdrawal of this rejection is respectfully requested.

Claims 6 and 7 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Impraim et al., in view of Prosnyak et al. (1994). The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill to combine the oligonucleotide method of Impraim et al. with the Prosnyak et al. method for modification of oligonucleotides with at least one 5-methylcytosine moiety. Applicants respectfully traverse this rejection.

As discussed *supra* in Section II, Impraim et al. fails to teach the limitations of the claimed invention. Therefore, the combination of a secondary reference (Prosnyak et al.) which teaches only methods for modifying oligonucleotides does not render the instant invention obvious. Withdrawal of this rejection is respectfully requested.

Claim 10 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Impraim et al., in view of Lundin et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill to combine the Impraim detection method with

the Lundin S1 nuclease to make the claimed invention. Applicants respectfully disagree with the Examiner's conclusions.

As discussed *supra* in Section II, the primary reference of Impraim et al. fails to teach the claimed invention. Therefore, the combination of Lundin et al., which teaches a method for screening large regions of DNA for structural changes, a very different method for a different purpose, cannot render the instant invention obvious. Withdrawal of this rejection is respectfully requested.

**IV. Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **January 30, 2002**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the Claims:**

Claim 11 has been canceled.

Claim 1 has been amended as follows:

1. A method for detecting or quantitating an oligonucleotide in a bodily fluid or extract, ~~comprising~~ consisting of the steps of:

a) contacting said fluid or extract with a probe complementary to said oligonucleotide so that both single-stranded and double-stranded oligonucleotide moieties are formed in said fluid or extract, wherein said probe comprises a detectable marker and a binding moiety;

b) placing said fluid or extract in contact with a solid support to which a binding partner of said binding moiety is attached so that both single-stranded and double-stranded oligonucleotide moieties present in said fluid or extract will be attached to said solid support;

c) contacting said fluid or extract with a single strand oligonucleotide-specific nuclease under conditions in which probe which is not hybridized to ~~said~~ form said double-stranded

oligonucleotide moieties is degraded and thus is no longer attached to said solid support; and

d) detecting a label associated with said marker wherein the presence of said label indicates the presence of said double-stranded oligonucleotide moieties bound to said solid support.